REMARKS

Claims 1-33 are pending in the instant application. Claims 1-33 have been rejected. Claims 1, 4, 14 and 15 have been amended. Claims 3 and 17-30 have been canceled. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1-3, 6-13, 21-26, 31 and 32 have been rejected under 35 U.S.C. 102(b) as being anticipated by Kole et al. (WO94/26887-A1). The Examiner suggests that this patent application teaches a method of altering the splicing of a pre-mRNA wherein an antisense oligonucleotide is hybridized to the pre-mRNA molecule to create a duplex under conditions that permit splicing and that the antisense is one that does not activate RNase H and is selected to block a member of the aberrant set of splice elements so that native protein is produced. Applicants respectfully disagree with the Examiner's conclusions.

Kole et al. (WO94/26887-A1)) disclose use of antisense oligonucleotides targeted to aberrant splice sites created by genetic mutations such as beta-thalassemia or cystic fibrosis. It

is shown that blocking a splice site with an antisense oligonucleotide will have a similar effect to mutation of the splice site, i.e., redirection of splicing. Nowhere does this patent application, however, teach or suggest a method of controlling behavior of a normal cell through modulating wild-type or native mRNA processing in the cell (see page 4 of the specification as filed). Further, nowhere does this patent application teach or suggest the modifications of the antisense oligonucleotides as now recited in the amended claims and as is taught in the specification as filed. In order to anticipate an invention, the reference must teach each and every limitation of the claimed invention (MPEP 2131). Clearly, teaching of use of antisense oligonucleotides to alter aberrant splicing is not the same as the present invention which teaches modulation of native mRNA processing in a cell such that the response of that cell to a stimulus is altered (see claim 1 and Examples 6-18 of the specification as filed). Further, this reference also fails to teach modifications of antisense compounds as now claimed. Accordingly, this reference cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

Claims 1, 2, 5-13 and 16-19 have been rejected under 35 U.S.C. 102(b) as being anticipated by Hodges et al. (1995). The Examiner suggests that Hodges et al. teach the construction, characterization and use of luciferase reporters to test the ability of antisense oligonucleotides to inhibit RNA splicing. Applicants respectfully disagree with the Examiner's conclusions.

Hodges and Crooke (1995) teach use of antisense oligonucleotides to modulate splicing, particularly aberrant splicing or splicing of mutant transcripts, in cell-free reporter systems. Using a luciferase reporter plasmid system, antisense compounds targeted to the 5' splice site, the 3' splice site or the branch point were shown to have activity to inhibit splicing of mutated or wild-type adenovirus pre-mRNA sequences in the reporter plasmid. Nowhere does this paper teach or suggest use of antisense oligonucleotides as a method to control the behavior of a cell to a stimulus by modulation of wild-type or native mRNA processing, which is the specific subject of the present invention. Further, nowhere does this reference teach modification of antisense compounds as is now claimed.

In order to anticipate an invention, the cited reference must teach each and every aspect of the claimed invention (MPEP 2131).

Clearly, teaching of use of antisense oligonucleotides to alter splicing in a reporter plasmid system, which is not a cell or a cell system with wild-type mRNA, is not the same as the present invention which teaches inhibition of mRNA cleavage in a cell such that the response of that cell to a stimulus is altered (see examples 6-18 of the specification as filed). Accordingly, this reference cannot anticipate the instant invention. In addition, the amended claims now specify certain modifications that are not taught in the instant invention. Therefore, withdrawal of this rejection is respectfully requested.

Claims 1, 6, 14-17 and 21-23 have been rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al. (WO9304701 A1). The Examiner suggests that Wu et al. teach use of oligonucleotide binding agents to target the polyadenylation signal of hepatitis B viral mRNA and then forming of a complex with its target mRNA. The Examiner suggests that this patent application teaches a method to block production of hepatitis virus in liver cells by use of a polylysine binding agent. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to make it clear that the targeted polyadenylation signal or site that is

targeted is found in a normal mammalian cell, not in a viral organism's genome. Nowhere does Wu et al. teach or suggest use of antisense oligonucleotides to target the polyadenylation site of mRNA in a cell other than a viral cell. Further, the claims have been amended to recite modifications of antisense compounds that are not taught or suggested by Wu et al. Accordingly, Wu et al. cannot anticipate the invention as now claimed. Withdrawal of this rejection is respectfully requested.

Claims 1, 2, 5-19, 29 and 30 have been rejected under 35 U.S.C. 102(b) as being anticipated by Moulds et al. (1995). The Examiner suggests that Moulds et al. teach design of antisense oligonucleotides having high affinity for RNA, thereby inactivating RNA via a non-RNAse H or steric block mechanism. Further, the Examiner suggests that this reference teaches use of an oligonucleotide targeting the 5' splice site of Tag RNA which results in 100% inhibition of splicing and blocked translation of RNA. Applicants respectfully disagree with the Examiner's conclusions.

It is respectfully pointed out that the instant invention is directed to methods using antisense compounds and antisense compounds that are targeted to mRNA, not RNA as provided in the

prior art reference. Moulds et al. teach biotinylated 2'-o-allylooligoribonucleotides incorporating 2-aminoadenine bases that are targeted to the U2 small nuclear RNA (snRNA), a component of the spliceosome, in HeLa nuclear extracts. Therefore, this prior art reference cannot anticipate the instant invention as suggested by the Examiner because it fails to teach antisense targeted to mRNA, as claimed. In order to anticipate an invention, the reference must teach each and every limitation of the claimed invention (MPEP 2131). Accordingly, withdrawal of this rejection is respectfully requested.

II. Double Patenting

Claims 1-33 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of U.S. Patent No. 6,210,892. The Examiner suggests that although the conflicting claims are not identical that are not patentably distinct from the referenced claims. Applicants have amended the claims of the instant invention such that they now recite modifications at least one 2'-guanidinium, 2'-carbamate, 2'-aminooxy, 3'-methylene phosphonate and those with at least one lysine or arginine at the C-terminus) that are not taught

in U.S. Patent 6,210,892. Therefore, the claims as amended are no longer obvious over the cited patent and withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Date: July 31, 2003

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